PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification [7]:
C12N 15/12, C07K 14/47, A61K 38/17, G01N 33/53, C12Q 1/68, C12N 15/62, C07K 16/18

A2

(11) International Publication Number: WO 00/53758

(43) International Publication Date: 14 September 2000 (14.09.00)

(21) International Application Number: PCT/US00/05841

(22) International Filing Date: 2 March 2000 (02.03.00)

(30) Priority Data:

PCT/US99/05028	8 March 1999 (08.03.99)	US
60/123,618	10 March 1999 (10.03.99)	US
60/123,957	12 March 1999 (12.03.99)	US
60/125,775	23 March 1999 (23.03.99)	US
60/128,849	12 April 1999 (12.04.99)	US
PCT/US99/08615	20 April 1999 (20.04.99)	US
60/131,445	28 April 1999 (28.04.99)	US
60/132,371	4 May 1999 (04.05.99)	US
60/134,287	14 May 1999 (14.05.99)	US
PCT/US99/12252	2 June 1999 (02.06.99)	US
60/141,037	23 June 1999 (23.06.99)	US
60/144,758	20 July 1999 (20.07.99)	US
60/145,698	26 July 1999 (26.07.99)	US
60/146,222	28 July 1999 (28.07.99)	US
PCT/US99/20111	1 September 1999 (01.09.99)	US
PCT/US99/20594	8 September 1999 (08.09.99)	US
PCT/US99/20944	13 September 1999 (13.09.99)	US
PCT/US99/21090	15 September 1999 (15.09.99)	US
PCT/US99/21547	15 September 1999 (15.09.99)	US
PCT/US99/23089	5 October 1999 (05.10.99)	US
60/162,506	29 October 1999 (29.10.99)	US
PCT/US99/28214	29 November 1999 (29.11.99)	US
PCT/US99/28313	30 November 1999 (30.11.99)	US
PCT/US99/28409	30 November 1999 (30.11.99)	US
PCT/US99/28301	1 December 1999 (01.12.99)	US
PCT/US99/28634	1 December 1999 (01.12.99)	US
PCT/US99/28551	2 December 1999 (02.12.99)	US
PCT/US99/28564	2 December 1999 (02.12.99)	US
PCT/US99/28565	2 December 1999 (02.12.99)	US
PCT/US99/30095	16 December 1999 (16.12.99)	US
PCT/US99/30999	20 December 1999 (20.12.99)	US
PCT/US99/31274	30 December 1999 (30.12.99)	US
PCT/US00/00219	5 January 2000 (05.01.00)	US
PCT/US00/00277	6 January 2000 (06.01.00)	US
PCT/US00/00376	6 January 2000 (06.01.00)	US
PCT/US00/03565	11 February 2000 (11.02.00)	US
PCT/US00/04341	18 February 2000 (18.02.00)	US
PCT/US00/04342	18 February 2000 (18.02.00)	US
PCT/US00/04414	22 February 2000 (22.02.00)	US

(71) Applicant *(for all designated States except US)*: GENENTECH, INC. [US/US]; 1 DNA Way, South San Francisco, CA 94080–4990 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ASHKENAZI, Avi, J. [US/US]; 1456 Tarrytown Street, San Mateo, CA 94402 (US). BAKER, Kevin, P. [GB/US]; 14006 Indian Run Drive, Damestown, MD 20878 (US). GODDARD, Audrey [CA/US]; 110 Congo Street, San Francisco, CA 94131 (US). GURNEY, Austin, L. [US/US]; 1 Debbie Lane, Belmont, CA 94002 (US). HEBERT, Caroline [US/US]; 1809 Vine Street, Berkeley, CA 94703 (US). HENZEL, William [US/US]; 3724 Southwood Drive, San Mateo, CA 94030 (US). KABAKOFF, Rhona, C. [BR/US]; 1084 Granada Drive, Pacifica, CA 94044 (US). LU, Yanmei [CN/US]; 1001 Continentals Way #206, Belmont, CA 94002 (US). PAN, James [CA/US]; 2705 Coronet Boulevard, Belmont, CA 94002 (US). PENNICA, Diane [US/US]; 2417 Hale Drive, Burlingame, CA 94010 (US). SHELTON, David, L. [US/US]; 5845 Clover Drive, Oakland, CA 94618 (US). SMITH, Victoria [AU/US]; 19 Dwight Road, Burlingame, CA 94010 (US). STEWART, Timothy, A. [US/US]; 465 Douglass Street, San Francisco, CA 94114 (US). TUMAS, Daniel [US/US]; 3 Rae Court, Orinda, CA 94563 (US). WATANABE, Colin, K. [US/US]; 128 Corliss Drive, Moraga, CA 94556 (US). WOOD, William, I. [US/US]; 35 Southdown Court, Hillsborough, CA 94010 (US). YAN, Minhong [CN/US]; 1910 Garden Drive #114, Burlingame, CA 94010 (US).

(74) Agents: SVOBODA, Craig, G. et al.; Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080–4990 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: COMPOSITIONS AND METHODS FOR THE TREATMENT OF IMMUNE RELATED DISEASES

(57) Abstract

The present invention relates to a composition containing novel proteins and methods for the diagnosis and treatment of immune related diseases.

surface of an antigen presenting cell and CD28 and CTLA-4 molecules expressed on the T cell surface effect 1 cell activation. Activated T cells express an increased number of cellular adhesion molecules, such as ICAM-1, integrins, VLA-4, LFA-1, CD56, *etc.*

T-cell proliferation in a mixed lymphocyte culture or mixed lymphocyte reaction (MLR) is an established indication of the ability of a compound to stimulate the immune system. In many immune responses, inflammatory cells infiltrate the site of injury or infection. The migrating cells may be neutrophilic, eosinophilic, monocytic or lymphocytic as can be determined by histologic examination of the affected tissues. Current Protocols in Immunology, ed. John E. Coligan, 1994, John Wiley & Sons, Inc.

Immune related diseases can be treated by suppressing the immune response. Using neutralizing antibodies that inhibit molecules having immune stimulatory activity would be beneficial in the treatment of immune-mediated and inflammatory diseases. Molecules which inhibit the immune response can be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

Summary of the Invention

The present invention concerns compositions and methods for the diagnosis and treatment of immune related disease in mammals, including humans. The present invention is based on the identification of proteins (including agonist and antagonist antibodies) which either stimulate or inhibit the immune response in mammals. Immune related diseases can be treated by suppressing or enhancing the immune response. Molecules that enhance the immune response stimulate or potentiate the immune response to an antigen. Molecules which stimulate the immune response can be used therapeutically where enhancement of the immune response would be beneficial. Such stimulatory molecules can also be inhibited where suppression of the immune response would be of value.

Neutralizing antibodies are examples of molecules that inhibit molecules having immune stimulatory activity and which would be beneficial in the treatment of immune related and inflammatory diseases. Molecules which inhibit the immune response can also be utilized (proteins directly or via the use of antibody agonists) to inhibit the immune response and thus ameliorate immune related disease.

Accordingly, the PRO polypeptides and anti-PRO antibodies and fragments thereof are useful for the diagnosis and/or treatment (including prevention) of immune related diseases. Antibodies which bind to stimulatory proteins are useful to suppress the immune system and the immune response. Antibodies which bind to inhibitory proteins are useful to stimulate the immune system and the immune response. The PRO polypeptides and anti-PRO antibodies also useful to prepare medicines and medicaments for the treatment of immune related and inflammatory diseases.

In one embodiment, the invention provides for isolated nucleic acid molecules comprising nucleotide sequences that encodes a PRO polypeptide.

In one aspect, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about

87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule encoding a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity, alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule comprising the coding sequence of a full-length PRO polypeptide cDNA as disclosed herein, the coding sequence of a PRO polypeptide lacking the signal peptide as disclosed herein, the coding sequence of an extracellular domain of a transmembrane PRO polypeptide, with or without the signal peptide, as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity,

alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity, alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule that encodes the same mature polypeptide encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein, or (b) the complement of the DNA molecule of (a).

In another aspect, the invention provides for isolated nucleic acid molecule comprising a nucleotide sequence encoding a PRO polypeptide with is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptides are disclosed herein. Therefore, soluble extracellular domains of the herein described PRO polypeptides are contemplated.

Another embodiment is directed to fragments of a PRO polypeptide coding sequence, or the complement thereof, that may find use as, for example, hybridization probes, for encoding fragments of a PRO polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-PRO polypeptide antibody or as antisense oligonucleotide probes. Such nucleic acid fragments are usually at least about 20 nucleotides in length, alternatively at least about 30 nucleotides in length, alternatively at least about 40 nucleotides in length, alternatively at least about 50 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 70 nucleotides in length, alternatively at least about 80 nucleotides in length, alternatively at least about 90 nucleotides in length, alternatively at least about 100 nucleotides in length, alternatively at least about 110 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 130 nucleotides in length, alternatively at least about 140 nucleotides in length, alternatively at least about 150 nucleotides in length, alternatively at least about 160 nucleotides in length, alternatively at least about 170 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 190 nucleotides in length, alternatively at least about 200 nucleotides in length, alternatively at least about 250 nucleotides in length, alternatively at least about 300 nucleotides in length, alternatively at least about 350 nucleotides in length, alternatively at least about 400 nucleotides in length, alternatively at least about 450 nucleotides in length, alternatively at least about 500 nucleotides in length, alternatively at least about 600 nucleotides in length, alternatively at least about 700 nucleotides in length, alternatively at least about 800 nucleotides in length, alternatively at least about 900 nucleotides in length, alternatively at least about 1000 nucleotides in length, alternatively at least about 1500 nucleotide in length, alternatively at least about 2000 nucleotides in length, alternatively at least about 2500 nucleotide in length, alternatively at least about 3000 nucleotide in length, alternatively at least about 4000 nucleotide in length, alternatively at least about 5000 nucleotides in length, or more, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel fragments of a nucleotide sequence encoding the respective PRO polypeptide may be determined in a routine manner by aligning the respective nucleotide encoding a PRO polypeptide with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which nucleotide sequence fragment(s) are novel. All such nucleotide sequences encoding the respective PRO polypeptides are contemplated herein. Also contemplated are the nucleotide molecules which encode fragments of the PRO polypeptides, preferably those polypeptide fragments that comprise a binding site for an anti-PRO polypeptide antibody.

In another embodiment, the invention provides isolated PRO polypeptides encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a certain aspect, the invention concerns an isolated PRO polypeptide, comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity, alternatively at least about 99% amino acid sequence identity to a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein.

In a further aspect, the invention concerns an isolated PRO polypeptide comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity, alternatively at least about 99% amino acid sequence identity to an amino acid sequence encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein.

In a further aspect, the invention concerns an isolated PRO polypeptide comprising an amino acid sequence scoring at least about 80% positives, alternatively at least about 81% positives, alternatively at least about 82% positives, alternatively at least about 83% positives, alternatively at least about 84% positives, alternatively at least about 85% positives, alternatively at least about 86% positives, alternatively at least about 87% positives, alternatively at least about 88% positives, alternatively at least about 89% positives, alternatively at least about 90% positives, alternatively at least about 91% positives, alternatively at least about 92% positives, alternatively at least about 93% positives, alternatively at least about 94% positives, alternatively at least about 95% positives, alternatively at least about 96% positives, alternatively at least about

97% positives, alternatively at least about 98% positives, alternatively at least about 99% positives when compared with the amino acid sequence of a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein.

In a specific aspect, the invention provides an isolated PRO polypeptide without the N-terminal signal sequence and/or the initiating methionine and is encoded by a nucleotide sequence that encodes such an amino acid sequence as hereinbefore described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the same from the cell culture.

In another aspect, the invention provides an isolated PRO polypeptide which is either transmembrane-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

In another embodiment, the invention provides vectors comprising DNA encoding any of the PRO polypeptides. Host cells comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli* or yeast. A process for producing any of the herein described polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired polypeptides and recovering the desired polypeptide from the cell culture.

In other embodiments, the invention provides chimeric molecules comprising any of the herein described polypeptides fused to a heterologous polypeptide or amino acid sequence. Examples of such chimeric molecules comprise any of the herein described polypeptides fused to an epitope tag sequence or a Fc region of an immunoglobulin.

In yet other embodiments, the invention provides oligonucleotide probes useful for isolating genomic and cDNA nucleotide sequences or as antisense probes, wherein those probes may be derived from any of the above or below described nucleotide sequences.

In yet another embodiment, the invention concerns agonists and antagonists of the PRO polypeptides, that mimic or inhibit one or more functions or activities of the PRO polypeptides. In a particular embodiment, the agonist or antagonist is an antibody that binds to the PRO polypeptides or a small molecule.

In another embodiment, the invention provides an antibody which specifically binds to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, humanized antibody, antibody fragment or single-chain antibody. In one aspect, the present invention concerns an isolated antibody which binds a PRO polypeptide. In another aspect, the antibody mimics the activity of a PRO polypeptide (an agonist antibody) or conversely the antibody inhibits or neutralizes the activity of a PRO polypeptide (an antagonist antibody). In another aspect, the antibody is a monoclonal antibody, which preferably has nonhuman complementarity determining region (CDR) residues and human framework region (FR) residues. The antibody may be labeled and may be immobilized on a solid support. In a further aspect, the antibody is an antibody fragment, a monoclonal antibody, a single-chain antibody, or an anti-idiotypic

Sequence Comparison A

```
ID   AAC58617 standard; cDNA; 957 BP.
XX
DE   Human PRO1343 protein UNQ698 encoding cDNA SEQ ID NO:179.
XX
PN   WO200053758-A2.
XX
PD   14-SEP-2000.
XX
PF   02-MAR-2000; 2000WO-US05841.
XX
PA   (GETH ) GENENTECH INC.
XX
PI   Ashkenazi AJ,  Baker KP,  Goddard A,  Gurney AL,  Hebert C,  Henzel W;
PI   Kabakoff RC,  Lu Y,  Pan J,  Pennica D,  Shelton DL,  Smith V;
PI   Stewart TA,  Tumas D,  Watanabe CK,  Wood WI,  Yan M;
XX
PS   Claim 23; Fig 77; 309pp; English.
XX
SQ   Sequence 957 BP; 241 A; 246 C; 303 G; 167 T; 0 other;
```

Alignment Scores:

Pred. No.:	5.9e-94	Length:	957
Score:	1279.00	Matches:	247
Percent Similarity:	100.00%	Conservative:	0
Best Local Similarity:	100.00%	Mismatches:	0
Query Match:	100.00%	Indels:	0
DB:	21	Gaps:	0

US-10-012-231A-248 (1-247) x AAC58617 (1-957)

```
Qy          1 MetHisLeuAlaArgLeuValGlySerCysSerLeuLeuLeuLeuLeuGlyAlaLeuSer 20
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         71 ATGCATCTTGCACGTCTGGTCGGCTCCTGCTCCCTCCTTCTGCTACTGGGGGCCCTGTCT 130

Qy         21 GlyTrpAlaAlaSerAspAspProIleGluLysValIleGluGlyIleAsnArgGlyLeu 40
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        131 GGATGGGCGGCCAGCGATGACCCCATTGAGAAGGTCATTGAAGGGATCAACCGAGGGCTG 190

Qy         41 SerAsnAlaGluArgGluValGlyLysAlaLeuAspGlyIleAsnSerGlyIleThrHis 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        191 AGCAATGCAGAGAGAGAGGTGGGCAAGGCCCTGGATGGCATCAACAGTGGAATCACGCAT 250

Qy         61 AlaGlyArgGluValGluLysValPheAsnGlyLeuSerAsnMetGlySerHisThrGly 80
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        251 GCCGGAAGGGAAGTGGAGAAGGTTTTCAACGGACTTAGCAACATGGGGAGCCACACCGGC 310

Qy         81 LysGluLeuAspLysGlyValGlnGlyLeuAsnHisGlyMetAspLysValAlaHisGlu 100
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        311 AAGGAGTTGGACAAAGGCGTCCAGGGGCTCAACCACGGCATGGACAAGGTTGCCCATGAG 370

Qy        101 IleAsnHisGlyIleGlyGlnAlaGlyLysGluAlaGluLysLeuGlyHisGlyValAsn 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        371 ATCAACCATGGTATTGGACAAGCAGGAAAGGAAGCAGAGAAGCTTGGCCATGGGGTCAAC 430

Qy        121 AsnAlaAlaGlyGlnAlaGlyLysGluAlaAspLysAlaValGlnGlyPheHisThrGly 140
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        431 AACGCTGCTGGACAGGCCGGGAAGGAAGCAGACAAAGCGGTCCAAGGGTTCCACACTGGG 490

Qy        141 ValHisGlnAlaGlyLysGluAlaGluLysLeuGlyGlnGlyValAsnHisAlaAlaAsp 160
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        491 GTCCACCAGGCTGGGAAGGAAGCAGAGAAACTTGGCCAAGGGGTCAACCATGCTGCTGAC 550
```

```
Qy        161 GlnAlaGlyLysGluValGluLysLeuGlyGlnGlyAlaHisHisAlaAlaGlyGlnAla 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        551 CAGGCTGGAAAGGAAGTGGAGAAGCTTGGCCAAGGTGCCCACCATGCTGCTGGCCAGGCC 610

Qy        181 GlyLysGluLeuGlnAsnAlaHisAsnGlyValAsnGlnAlaSerLysGluAlaAsnGln 200
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        611 GGGAAGGAGCTGCAGAATGCTCATAATGGGGTCAACCAAGCCAGCAAGGAGGCCAACCAG 670

Qy        201 LeuLeuAsnGlyAsnHisGlnSerGlySerSerSerHisGlnGlyGlyAlaThrThrThr 220
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        671 CTGCTGAATGGCAACCATCAAAGCGGATCTTCCAGCCATCAAGGAGGGGCCACAACCACG 730

Qy        221 ProLeuAlaSerGlyAlaSerValAsnThrProPheIleAsnLeuProAlaLeuTrpArg 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        731 CCGTTAGCCTCTGGGGCCTCAGTCAACACGCCTTTCATCAACCTTCCCGCCCTGTGGAGG 790

Qy        241 SerValAlaAsnIleMetPro 247
              |||||||||||||||||||
Db        791 AGCGTCGCCAACATCATGCCC 811
```

```
ID   AAC58617 standard; cDNA; 957 BP.
XX
DT   29-JAN-2001  (first entry)
XX
DE   Human PRO1343 protein UNQ698 encoding cDNA SEQ ID NO:179.
XX
OS   Homo sapiens.
XX
PN   WO200053758-A2.
XX
PD   14-SEP-2000.
XX
PF   02-MAR-2000; 2000WO-US05841.
XX
PI   Ashkenazi AJ,  Baker KP,  Goddard A,  Gurney AL,  Hebert C,  Henzel W;
PI   Kabakoff RC,  Lu Y,  Pan J,  Pennica D,  Shelton DL,  Smith V;
PI   Stewart TA,  Tumas D,  Watanabe CK,  Wood WI,  Yan M;
XX
DR   WPI; 2000-572271/53.
DR   P-PSDB; AAB33452.
XX
PT   Sixty four PRO polypeptides, useful in the diagnosis and treatment of
PT   immune related disorders, e.g. systemic lupus erythematosis, rheumatoid
PT   arthritis, osteoarthritis, thyroiditis and diabetes mellitus -
XX
PS   Claim 23; Fig 77; 309pp; English.
XX
SQ   Sequence 957 BP; 241 A; 246 C; 303 G; 167 T; 0 other;
```

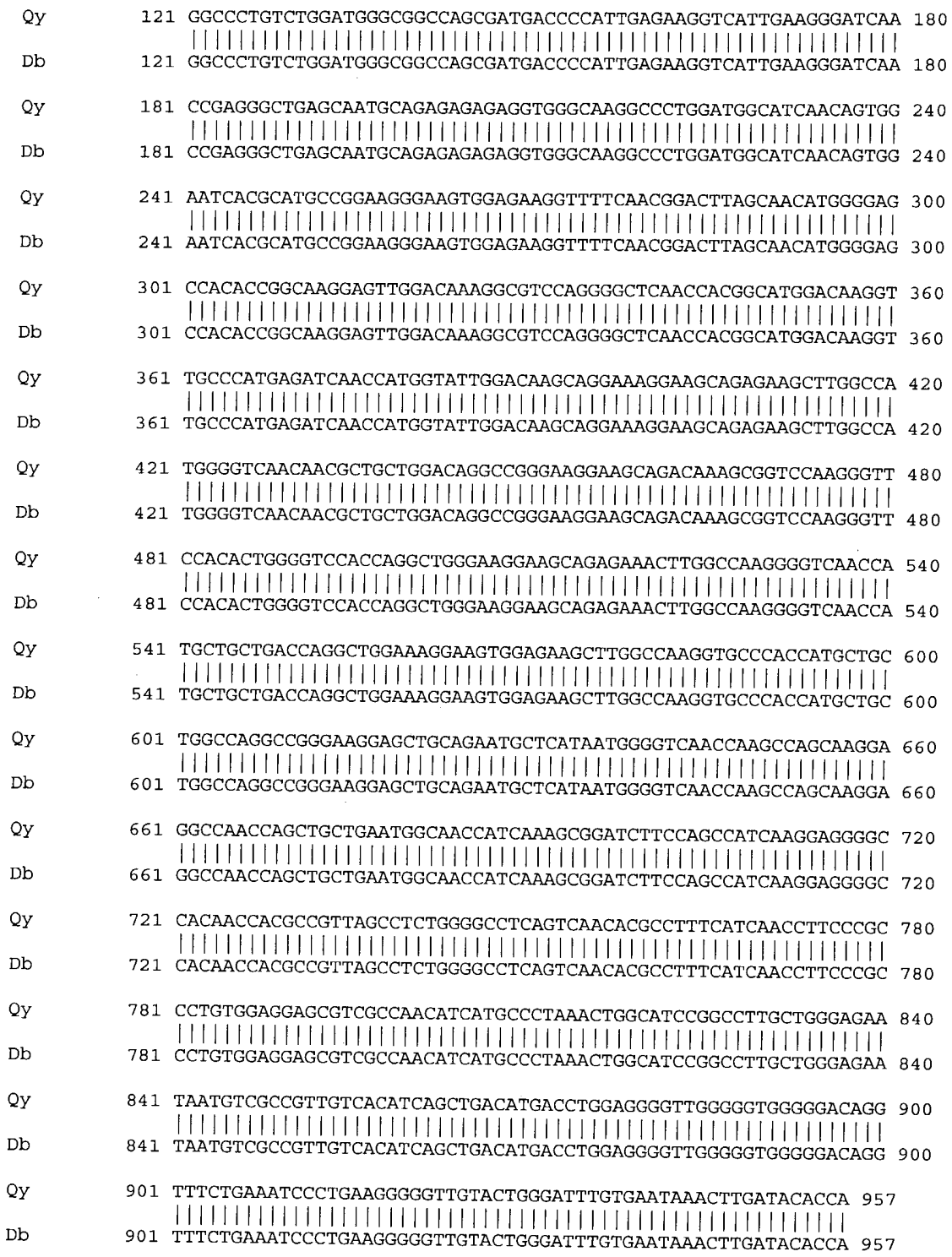
Sequence Comparison B

```
  Query Match           100.0%;  Score 957;  DB 21;  Length 957;
  Best Local Similarity  100.0%;  Pred. No. 1.6e-245;
  Matches  957;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GGGAGAGAGGATAAATAGCAGCGTGGCTTCCCTGGCTCCTCTCTGCATCCTTCCCGACCT 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 GGGAGAGAGGATAAATAGCAGCGTGGCTTCCCTGGCTCCTCTCTGCATCCTTCCCGACCT 60

Qy         61 TCCCAGCAATATGCATCTTGCACGTCTGGTCGGCTCCTGCTCCCTCCTTCTGCTACTGGG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 TCCCAGCAATATGCATCTTGCACGTCTGGTCGGCTCCTGCTCCCTCCTTCTGCTACTGGG 120
```

B


Qy 121 GGCCCTGTCTGGATGGGCGGCCAGCGATGACCCCATTGAGAAGGTCATTGAAGGGATCAA 180
Db 121 GGCCCTGTCTGGATGGGCGGCCAGCGATGACCCCATTGAGAAGGTCATTGAAGGGATCAA 180
Qy 181 CCGAGGGCTGAGCAATGCAGAGAGAGAGGTGGGCAAGGCCCTGGATGGCATCAACAGTGG 240
Db 181 CCGAGGGCTGAGCAATGCAGAGAGAGAGGTGGGCAAGGCCCTGGATGGCATCAACAGTGG 240
Qy 241 AATCACGCATGCCGGAAGGGAAGTGGAGAAGGTTTTCAACGGACTTAGCAACATGGGGAG 300
Db 241 AATCACGCATGCCGGAAGGGAAGTGGAGAAGGTTTTCAACGGACTTAGCAACATGGGGAG 300
Qy 301 CCACACCGGCAAGGAGTTGGACAAAGGCGTCCAGGGGCTCAACCACGGCATGGACAAGGT 360
Db 301 CCACACCGGCAAGGAGTTGGACAAAGGCGTCCAGGGGCTCAACCACGGCATGGACAAGGT 360
Qy 361 TGCCCATGAGATCAACCATGGTATTGGACAAGCAGGAAAGGAAGCAGAGAAGCTTGGCCA 420
Db 361 TGCCCATGAGATCAACCATGGTATTGGACAAGCAGGAAAGGAAGCAGAGAAGCTTGGCCA 420
Qy 421 TGGGGTCAACAACGCTGCTGGACAGGCCGGGAAGGAAGCAGACAAAGCGGTCCAAGGGTT 480
Db 421 TGGGGTCAACAACGCTGCTGGACAGGCCGGGAAGGAAGCAGACAAAGCGGTCCAAGGGTT 480
Qy 481 CCACACTGGGGTCCACCAGGCTGGGAAGGAAGCAGAGAAACTTGGCCAAGGGGTCAACCA 540
Db 481 CCACACTGGGGTCCACCAGGCTGGGAAGGAAGCAGAGAAACTTGGCCAAGGGGTCAACCA 540
Qy 541 TGCTGCTGACCAGGCTGGAAAGGAAGTGGAGAAGCTTGGCCAAGGTGCCCACCATGCTGC 600
Db 541 TGCTGCTGACCAGGCTGGAAAGGAAGTGGAGAAGCTTGGCCAAGGTGCCCACCATGCTGC 600
Qy 601 TGGCCAGGCCGGGAAGGAGCTGCAGAATGCTCATAATGGGGTCAACCAAGCCAGCAAGGA 660
Db 601 TGGCCAGGCCGGGAAGGAGCTGCAGAATGCTCATAATGGGGTCAACCAAGCCAGCAAGGA 660
Qy 661 GGCCAACCAGCTGCTGAATGGCAACCATCAAAGCGGATCTTCCAGCCATCAAGGAGGGGC 720
Db 661 GGCCAACCAGCTGCTGAATGGCAACCATCAAAGCGGATCTTCCAGCCATCAAGGAGGGGC 720
Qy 721 CACAACCACGCCGTTAGCCTCTGGGGCCTCAGTCAACACGCCTTTCATCAACCTTCCCGC 780
Db 721 CACAACCACGCCGTTAGCCTCTGGGGCCTCAGTCAACACGCCTTTCATCAACCTTCCCGC 780
Qy 781 CCTGTGGAGGAGCGTCGCCAACATCATGCCCTAAACTGGCATCCGGCCTTGCTGGGAGAA 840
Db 781 CCTGTGGAGGAGCGTCGCCAACATCATGCCCTAAACTGGCATCCGGCCTTGCTGGGAGAA 840
Qy 841 TAATGTCGCCGTTGTCACATCAGCTGACATGACCTGGAGGGGTTGGGGGTGGGGGACAGG 900
Db 841 TAATGTCGCCGTTGTCACATCAGCTGACATGACCTGGAGGGGTTGGGGGTGGGGGACAGG 900
Qy 901 TTTCTGAAATCCCTGAAGGGGGTTGTACTGGGATTTGTGAATAAACTTGATACACCA 957
Db 901 TTTCTGAAATCCCTGAAGGGGGTTGTACTGGGATTTGTGAATAAACTTGATACACCA 957